(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 April 2003 (24.04.2003)

PCT

(10) International Publication Number
WO 03/032924 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/33526

(22) International Filing Date: 18 October 2002 (18.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0125061.2	18 October 2001 (18.10.2001)	GB
60/350,121	2 November 2001 (02.11.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL TIBOLONE FORMULATIONS

(57) Abstract: The invention relates to the field of synthetic steroids and particularly to oestrene derivatives. Specifically, the invention relates to stabilized compositions of tibolone (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, and to methods of preparing the same.

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NOVEL TIBOLONE FORMULATIONS

INVENTORS: T. Brennan, A.J. Woolfe

FIELD OF THE INVENTION

[001] This invention relates to the field of synthetic steroids and particularly to oestrene derivatives. Specifically, the invention relates to stabilized pharmaceutical compositions and dosage forms of tibolone (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, and to methods of preparing the same.

BACKGROUND OF THE INVENTION

[002] Tibolone ($C_{21}H_{28}O_2$) is a synthetic steroid of the oestrane series (a $\Delta^{5(10)}$-oestrene derivative) known to have combined oestrogenic, progestogenic and androgenic characteristics. Tibolone is structurally related to the progestogens norethindrone and norethynodrel. For a general review of the pharmacology of tibolone see van der Vies, Maturitas Suppl. 1:15-24 (1987). Tibolone is used *inter alia*, in pharmacological preparations having gonadomimetic, ovulation-inhibiting or immuno-modulatory action (see Tax *et al.*, Progress in Basic Clinical Pharmacology 6:143-159 (1991) and Tax *et al.*, Maturitas Suppl. 1:3-13 (1987)) for a general review of the clinical pharmacology of tibolone).

[003] Unfortunately, tibolone dosage forms (e.g., tablets or capsules) are both difficult to prepare and are plagued by instability problems. One of the tibolone polymorphs generally found in tibolone preparations, particularly in preparations which are not enriched for a particular polymorph, has been shown to be difficult to dissolve. In addition, the resulting formulations obtained generally suffer from limited storage stability especially under dry conditions. The inherent stability is due to the presence of an impurity (*i.e.*, (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one), which increases during the preparation of pharmaceutical dosage units. Unfortunately, the amount of the destabilizing impurity also increases during storage by conversion of (7α, 17α)-17-hydroxy-7-

methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one into (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one by acid catalyzed isomerization.

[004] Various attempts have been reported to try to overcome these problems. Hence, for example EP 159739 discloses a number of tablet formulations of tibolone containing conventional tablet excipients. EP 159739 however, does not address the stability problems associated with tibolone formulations.

[005] EP 389035 describes the production of two pure polymorphic forms (forms I and II) of tibolone. This patent further postulates that polymorph I is appreciably more stable than the polymorph II. Allegedly more stable preparations comprising a crystalline pure or virtually pure form which is completely or, virtually completely free from the other crystalline form are disclosed and are presently marketed under the mark LIVIAL™ in the United Kingdom.

[006] WO 98/47517 describes the use of a high percentage (above 10%) of starch in a tibolone formulation and claims that better stability is obtained, particularly under relatively dry storage conditions or with lower doses of tibolone.

[007] Although the approaches found in the art may to some extent improve some of the problems still associated with tibolone formulation (*i.e.*, stability and solubility), there remains a need to identify compositions and methods better suited to arrive to stable as well as soluble tibolone preparations.

SUMMARY OF THE INVENTION

[008] The invention meets the present needs by providing compositions comprising tibolone and a pH-adjusting agent which are stable.

[009] Additional aspects of the invention relate to methods of preparing tibolone compositions comprising a pH-adjusting agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[010] Figure 1 is a representation of a graph showing the dissolution profiles of (a) representative formulations RDT0328 prepared by wet granulation, and RDT0329 prepared by dry granulation, according to the invention (see specifics for Formulation A in example 3 hereinafter) at time 0 and after 6 weeks of storage at 40°C and 75% relative humidity, and of (b) IP0022 and IP0047, both are polymorph I-enriched formulations (see EP 389035).

[011] Figure 2 is a representation of a graph showing the stability profiles of (a) representative formulation A according to the invention (see Example 3 hereinafter) at both time 0, after 6 weeks, and after 4 months of storage at 40°C and 75% relative humidity, and of (b) Formulation B which is polymorph I-enriched (see EP 389035).

DETAILED DESCRIPTION OF THE INVENTION

[012] Surprisingly, it has now been discovered that the inclusion of a pH-adjusting agent increases the stability of formulations of oestrene derivatives such as tibolone formulations.

[013] Moreover it has been found that even formulations containing more than threshold percentages of polymorph II --which has been reported in the literature to be associated with instability and solubility problems-- may be stabilized by the inclusion of a pH adjusting agent in the formulation. The aim of the present

invention is therefore to obtain compositions which are stable, soluble, and do not necessarily require pure or quasi-pure crystalline preparations.

[014] The patents, published applications, and scientific literature referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

[015] Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference is made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

[016] Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard works setting forth the general principles of pharmaceutical dosage form preparation techniques including granulation, mixing, coating techniques include for example, Lachman *et al.* Eds., The Theory and Practice of Industrial Pharmacy, 3rd Ed., (1986), and Lieberman *et al.*, Eds. Pharmaceutical Dosage Forms, Marcel Dekker Inc., New York and Basel (1989).

[017] As used in this specification, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise. Similarly, in the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise.

[018] As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least." When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

[019] The invention provides pharmaceutical compositions containing tibolone in admixture with one or more excipients, and a pH adjusting agent. The term "pH adjusting agent" is used to denote an agent which when mixed with one or more compounds in a formulation adjusts the acidity of the formulation and may additional have antioxidative properties. In some embodiments the pH adjusting agent may have synergistic antioxidative properties with other compounds in the formulation to which the pH adjusting agent is added. The pH adjusting agent may be the salt of an acid, particularly a weak acid, such as a carboxylic acid. Suitable salts of carboxylic acids include salts of citric, fumaric, acetic, tartaric, maleic, succinic or benzoic acid. Particular examples of pH adjusting agents are salts of polybasic acids, such as the acid salts of citric acid, for example monosodium dihydrogen citrate, disodium hydrogen citrate and especially sodium citrate. The polybasic acid may also be an inorganic polybasic acid. Salts of inorganic polybasic acids that may be mentioned include phosphate, hydrogen phosphate, carbonate and hydrogen carbonate, in particular potassium and especially sodium hydrogen carbonate (also known as sodium bicarbonate). Borates, for example sodium borate, may also be mentioned.

[020] Where the pH adjusting agent is the salt of an acid, the cation may be inorganic or organic. Suitable inorganic cations include the alkali metals, e.g.,

sodium and potassium, and the alkali earths, in particular magnesium and calcium. Organic cations include quaternary ammonium salts.

[021] Alternatively, the pH adjusting agent may be the salt of a weak base, for example, an ammonium salt, such as ammonium chloride. The pH adjusting agent may also be a buffering agent, particularly an organic buffering agent. A particular buffering agent that may be mentioned is Tris buffer, tris-(hydroxymethyl)methyl ammonium chloride.

[022] One of skills in the art will appreciate that the compositions of the invention may be solid as well as liquid depending on the specific exigencies and circumstances.

[023] In certain embodiments the compositions of the invention are liquid compositions comprising a 1%w/v aqueous solution of the pH adjusting agent having a pH of from about 4 to about 10, more preferably from about 6 to about 9 and most preferably from about pH 7 to about pH 9.

[024] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

[025] Examples of pH of a 1%w/v aqueous solutions of suitable pH adjusting agents are as follows:

Table I

1%w/v aqueous solution	Sodium Bicarbonate	pH 8.2
1%w/v aqueous solution	Sodium Citrate	pH 8.75

[026] Insofar as both solid as well as liquid compositions are contemplated, it is understood that the pH adjusting agent according to the invention may be in a solid form such as a crystalline or a dry/fine powder form.

[027] The dosage unit forms exemplified hereinafter include 2.5 mg of tibolone in a tablet form or 100 mg of a pharmaceutically acceptable powder in capsules (*i.e.*, 2.5%). However, there is a long-felt need to provide lower dosage forms to fine-tune therapeutic regimens to individual patients' needs. Unfortunately, simply lowering the tibolone content results in a dramatic and prohibitive decrease in stability and concurrent shelf life. Inclusion of the pH adjusting agent according to the invention is therefore also useful to stabilize formulations having a low (i.e., less than 2.5 mg) tibolone content.

[028] In certain embodiments of the invention, the ratio of pH adjusting agent to tibolone is from about 10 parts agent to about 1 part tibolone to about 0.01 parts agent to about 1 part tibolone.

[029] For oral administration, the compositions of the invention may be presented as discrete units such as capsules, caplets, gelcaps, cachets, pills, or tablets each containing a predetermined amount of the active ingredient as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, *etc.*

[030] Alternately, administration of a composition of all of the aspects of the present invention may be effected by liquid solutions, suspensions or elixirs, powders, lozenges, micronized particles and osmotic delivery systems. Pharmaceutical dosage forms especially contemplated in the present invention include solid dosage form such as tablets or capsules, as well as other dry (non-solid) or liquid forms. One of skill in the art will appreciate that the compositions of the invention are easily adapted without undue experimentation for administration by other routes.

[031] A pharmaceutical oral dosage form, such as for example a tablet, may be made by a variety of methods known in the art (see e.g., Lachman *et al.* (supra) and Lieberman *et al.* *(supra)* compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally coated or scored and may be formulated to provide a slow or controlled release of the active ingredient therein.

[032] The methods set forth in the examples provided hereinafter are merely representative examples to illustrate some of the possible ways available and are not meant to limit the scope of the invention.

[033] The compositions according to the invention may be prepared by the simple addition of the active agent (*i.e.,* tibolone) to the powder, tablet, capsule or granule mix with all the other components described herein.

[034] In a further embodiment, tibolone, the pH adjusting agent are mixed together and then granulated with a solution of binder in water or organic solvent e.g., an alcohol. Any auxiliary components e.g., starch may be mixed subsequently as well. The binder may in principle be any suitable pharmaceutical binder such as any cellulose derivative e.g., hydroxy propyl methyl cellulose or polymers such as polyvinyl pyrrolidone. In certain embodiments, the compositions of the invention may further include components useful to achieve the release of tibolone over time or to delay the release of tibolone (e.g., extended release, continued release or delayed release) such as for examplehydroxypropylmethylcellulose, hydroxy propylcellulose, ethylcellulose, hydroxyethylcellulose, castor oils, vegetable oils, xanthan gum, and waxes.

[035] In some embodiments, the compositions of the invention further comprise antioxidant compounds such as for example vitamin E, vitamin C, carotene, ascorbyl palmitate, ascorbyl stearate, propylgallate, lactic acid, and erythrobic acid.

[036] In particular a starch paste or other starch derivative is particularly preferred. In addition the binder compound could be added to the dry mix and granulated with pure water or solvent.

[037] It will be understood that in all embodiments of this invention conventional pharmaceutical excipients can be added to the compositions.

[038] The compositions according to the invention are optionally formulated with any of the well known pharmaceutically acceptable carriers, including diluents and excipients (see Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA 1990, Remington: The Science and Practice of Pharmacy, Lippincott, Williams & Wilkins, 1995, and The Handbook of Pharmaceutical Excipients, 3rd Ed., American Pharmaceutical Association and Pharmaceutical Press, 2000). This includes bulking agents such as sugars, e.g., lactose; cellulose derivatives e.g., microcrystalline cellulose; calcium salts e.g., calcium phosphate or calcium sulphate; disintegrants e.g., sodium starch glycolate, crosscarmellose; lubricants e.g., magnesium stearate, sodium stearyl fumarate and surfactants, and wetting agents, e.g., sodium lauryl sulphate, conventional poloxamers, polyethylene glycols, sodium tetradecylsulphate, and sorbitan esters.

[039] Other pharmaceutical excipients such as colors, flavors, *etc.* may also be added. While the type of pharmaceutically acceptable carrier/vehicle employed in generating the compositions of the invention will vary depending upon the mode of administration of the composition to a mammal, generally pharmaceutically acceptable carriers are physiologically inert and non-toxic. Formulations of compositions according to the invention may contain more than one active ingredient as well any other pharmacologically active ingredient useful for the treatment of the symptom/condition being treated.

EXAMPLES

[040] The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein.

Example 1

Preparation of Tibolone/Sodium Bicarbonate Formulations

[041] This example is provided to illustrate the preparation of a representative solid form tibolone formulation as described in more details heretofore. 2.5g of tibolone (obtained from Chemo Iberia, Italy) was admixed and triturated with 2.5g of sodium bicarbonate (Industriale Chimica s.r.l, Spain). This preparation was subsequently blended with 84g of lactose (Merck KGaA, Germany), 10g of starch (Colorcon, UK), and 1 g of magnesium stearate (Merck KGaA, Germany). The blend was then compressed into tablets of 100mg each, containing 2.5mg of tibolone. Samples were analyzed (λ= 200-240nm) to identify conjugated impurities (here identified as RC01 and RC04).

Table II

	RC04	RC01	TOTAL IMPURITY
Formulation without Sodi	1.32%	2.98%	7.47%
Bicarbonate			
100g batch with Sodium Bicarbonate	1.69%	1.48%	5.61%

Example 2

Preparation of Tibolone/Sodium Citrate Formulations

[042] This example is provided to illustrate the preparation of representative tibolone blends as described in more details heretofore. 2.5g of tibolone (obtained from Industriale Chimica SRL, Italy) was admixed and triturated with 2.5g of sodium citrate (Merck KgaA, Germany) and 5g of starch. This preparation was subsequently granulated with 5% solution of hydroxy propylmethyl cellulose in

water, and then dried. Granules were then milled and dry blended with 85g of lactose, 2g of sodium starch glycolate, and 1g of magnesium stearate. The blend was then compressed into tablets of 100mg each, containing 2.5mg of tibolone. Samples were analyzed (λ= 200-240nm) to identify conjugated impurities (here identified as RC01 and RC04).

Table III

	RC04	RC01	TOTAL IMPURITY
Formulation without Sodi Citrate	1.32%	2.98%	7.47%
100g batch with Sodium Citrate	1.78%	1.22%	5.29%
400g batch with Sodium Citrate	1.58%	1.62%	5.65%

[043] In another experiment a tibolone/sodium citrate formulation was prepared essentially as described in the above paragraph and further comprising standard pharmaceutical excipients as described in more details above. The final 2.5 mg tibolone unit dose (Formulation A) form included:

Table IV

Formulation A Composition

Tibolone		2.5mg
Lactose		86.1mg
Lactose monohydrate (200 mesh)	52.775	
Spray dried lactose (dried compression grade)	33.33	
Pregelatinized starch		8.0mg
Ascorbyl palmitate		0.2mg
Sodium Citrate		0.69mg
Sodium Lauryl Sulphate		0.005mg
Croscarmellose Sodium		2.0mg
Mg Stearate		0.5mg

Example 3

Solubility of Tibolone Preparations

[044] It has been observed that tibolone preparations which have not been enriched for a particular polymorph (i.e., polymorph I) are plagued by an inherent lower solubility hindering their value for pharmaceutical purposes. To ascertain that the compositions of the invention are soluble, a series of dissolution tests were performed including the one included hereinafter for illustrative purposes. In this experiments the % dissolution for Formulation A (see Example 3 above) and Formulation B which is polymorph I-enriched (see EP 389035) were compared (for both wet and dry granulation methodologies).

[045] As shown in Figure 1, the dissolution profiles of (a) representative formulations RDT0328 prepared by wet granulation, and RDT0329 prepared by dry granulation, according to the invention (see specifics for Formulation A in example 3 hereinafter) at time 0 and after 6 weeks of storage at 40°C and 75% relative humidity, were comparable to the dissolution profiles observed for (b) Formulation B samples IP0022 and IP0047 (both are polymorph I-enriched formulations (see EP 389035)).

Example 4

Analytical Evaluation of Tibolone Preparations--Stability

[046] This example is provided to evidence the stability of the compositions according to the invention. For this purpose, the tibolone preparation Formulation A of Example 3 above was analyzed and further characterized. It was established that the tibolone of the preparation of Example 3 had a polymorphic ratio of 85% form I, and 15% of form II. It was found that there was no detectable transition from form II to form I upon prolonged storage. To test and compare the stability of the formulations according to the invention, Formulation A according to the invention (see Example 3, *supra*) was tested at both time 0, after 6 weeks, and after 4 months of storage at 40°C and 75% relative humidity, and of (b) Formulation B which is polymorph I-enriched (see EP 389035).

[047] The specific dissolution parameters for this set of experiments were as follows:

Apparatus:	Paddles
Rotation Speed:	75rpm
Dissolution Medium:	0.25% w/w sodium dodecyl (Lauryl) sulphate
Medium Volume:	900ml
Medium Temperature:	37°C ± 0.5°C
Detection:	UV @ 210nm
Sampling Times:	15mins

Table V

	FORMULATION B	FORMULATION A			
		TIME ZERO	3 WEEKS	6 WEEKS	4 MONTHS
ASSAY	96.9% (99.7mg)	112.4% (110.0mg)	99.3% (97.6mg)	96.7% (95.3mg)	95.3% (91.7mg)
DISSOLUTION AT 15 MINS	100% (100mg)	108% (106mg)	N/T	88% (92.5mg)	91% (95.0mg)
TOTAL RELATED SUBSTANCE	5.21%	1.03%	1.57%	1.34%	3.2%

[047] As shown in Figure 2 the stability of Formulation A preparations according to Example 3 were comparable to that observed for polymorph I-enriched preparations reported to be stable (see EP 389035) even after 4 month under accelerated storage conditions.

[048] Similarly, sample formulations matching those described in Examples 1 and 2 but omitting the pH adjusting agents (*i.e.*, sodium citrate and sodium bicarbonate) were included as well as samples as negative controls. These tests also showed that the presence of the pH adjusting agents stabilized the formulations (data not shown).

Example 5

Pharmacokinetic Studies of Representative Tibolone Compositions

[049] To illustrate the properties of the compositions according to the invention, in a pilot study, several subjects received two single oral administration of 2.5mg tibolone as the test and reference formulations according to a cross-over design. Each administration was separated by a two weeks wash out period. Standard bioavailability studies demonstrate that the active ingredient (i.e., tibolone) in the compositions disclosed herein reaches its maximal concentration (t_{max}) within published ranges, that it is also biologically converted to its isomeric form, and that the AUC values are within accepted ranges for bioequivalence (data not shown). Pharmacokinetic parameters for tibolone and Δ4-tibolone are calculated according to standard methods described in the literature.

Equivalents

[050] Reference is made hereinafter in detail to specific embodiments of the invention. While the invention will be described in conjunction with these specific embodiments, it will be understood that it is not intended to limit the invention to such specific embodiments. On the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims. In the instant description, numerous specific details are set forth in order to provide a thorough understanding of the present invention. The present invention may be practiced without some or all of these specific details. In other instances, well known process operations have not been described in detail, in order not to unnecessarily obscure the present invention

What is claimed is:

1. A composition comprising tibolone in admixture with one or more excipients, and a pH adjusting agent.

2. A composition according to claim 1, wherein the pH adjusting agent is a salt of an acid.

3. A composition according to claim 2, wherein the acid is a weak acid.

4. A composition according to claim 3, wherein the acid is a carboxylic acid.

5. A composition according to claim 2 or 3, wherein the acid is citric, acetic tartaric, fumaric, maleic, succinc or benzoic.

6. A composition according to claim 2, wherein the acid is a polybasic acid.

7. A composition according to claim 6, wherein the acid is an inorganic polybasic acid.

8. A composition according to claim 7, where in the salt of the polybasic acid is a phosphate, a hydrogen phosphate, a sulphate, a hydrogen sulphate, a carbonate or a hydrogen carbonate.

9. A composition according to claim 2, wherein the cation of the salt is an inorganic cation.

10. A composition according to claim 5, wherein the inorganic cation is sodium, potassium, magnesium or calcium.

11. A composition according to claim 2, wherein the cation of the salt is an organic cation.

12. A composition according to claim 1, wherein the pH adjusting agent is a buffer.

13. A composition according to claim 1 or 12, wherein the pH adjusting agent is tris-(hydroxymethyl) methyl ammonium chloride.

14. A composition according to any one of claims 1, wherein the composition is a solid dosage form.

15. A composition according to claim 1, further comprising a binder selected from the group consisting of starch, pre-gelatinized starch, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and polyvinyl pyrrolidone.

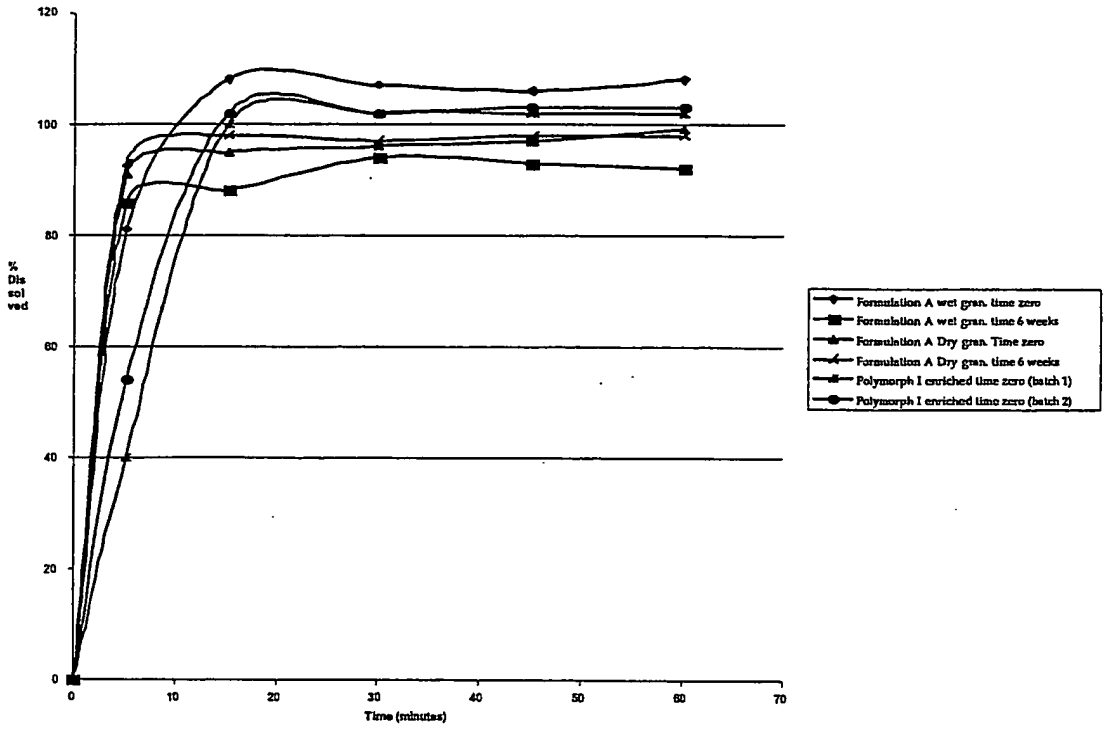
120
100
80
60
40
20
0
% Dissolved
0
10
20
30
40
50
60
70
Time (minutes)
Formulation A wet gran. time zero
Formulation A wet gran. time 6 weeks
Formulation A Dry gran. Time zero
Formulation A Dry gran. time 6 weeks
Polymorph I enriched time zero (batch 1)
Polymorph I enriched time zero (batch 2)

Figure 1

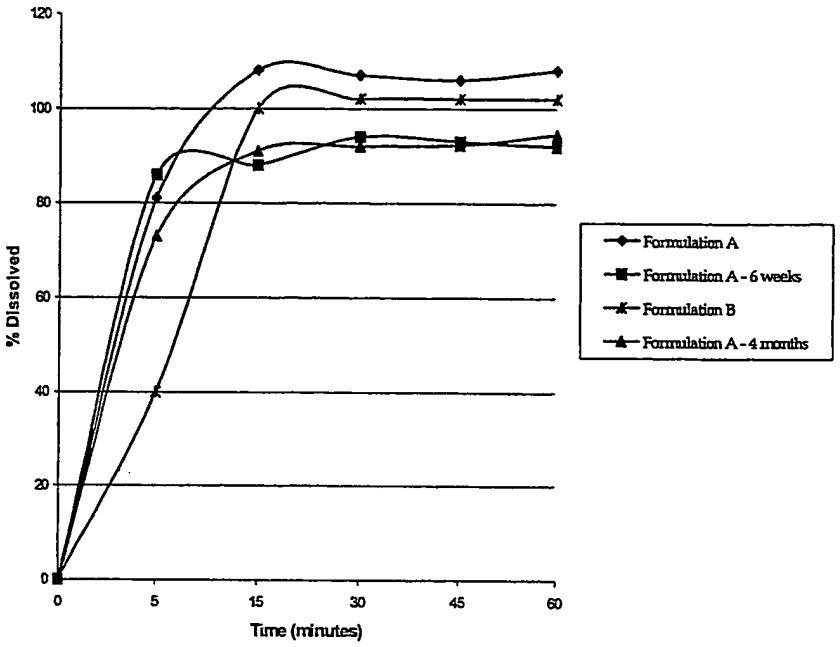
120
100
80
60
40
20
0
% Dissolved
0
5
15
30
45
60
Time (minutes)
Formulation A
Formulation A - 6 weeks
Formulation B
Formulation A - 4 months

Figure 2